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427.046

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	:	R. Desai
D. BIGG et al	:	
Serial No.: 09/806,952	:	Group: 1625
Filed: April 5, 2001	:	
For: OPTICALLY...ANALOGUES	:	

475 Park Avenue South
New York, N.Y. 10016
August 24, 2004

BRIEF ON APPEEAL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

REAL PARTY IN INTEREST

The real party in interest is Societe De Conseils De Recherches D'Applications Scientifiques by means of an assignment recorded in the Patent Office.

RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to Appellant, the Appellants' legal representative or assignee which would directly affect to be directly affected by or have a bearing on the Board's decision in the pending appeal.

STATUS OF THE CLAIMS

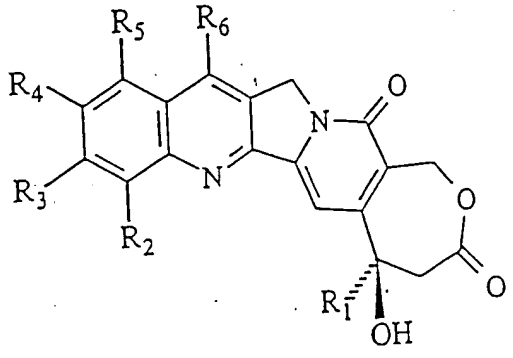
The claims remaining in the application are claims 5, 24, 26 and 27, all other claims having been cancelled.

STATUS OF THE AMENDMDENTS

The response of July 13, 2004 was considered by the Examiner but was deemed not to put the application in condition for allowance.

SUMMARY OF THE INVENTION

The invention is directed to compounds of the formula



(II_A)

wherein R_1 through R_5 are as indicated in the claims and R_6 is $-(CH_2)_m\text{-}SiR_7R_8R_9$ wherein R_7, R_8 and R_9 are individually lower alkyl and are non-toxic, pharmaceutically acceptable salts and a method of treating tumors with the same compounds.

THE PRIOR ART

Hausheer et al	WO 98/07727	2/26/98
Lavergne et al	Journal of Medicine	1998

The Hausheer et al reference relates to camptothecins wherein R_1 has many possible substituents. R_1 can be acyl of an alkanoic acid and various other substituents and it is stated that the compunds are highly lipophilic, lactone stable and do not require metabolic activation and are useful as anti-neoplastic compounds.

The Lavergne et al reference, which is Applicants' own publication, is directed to hcpt compounds which do not contain any Si group.

THE ISSUES

All of the claims stand rejected as being obvious over a combination of the Hausheer et al and Lavergne et al references and the Examiner states that the Lavergne et al reference clearly teaches that hcpt and cpt are equivalent and that one skilled in the art, from the teaching of Hausheer et al, that Si containing group on the same position makes it more soluble deems it would be obvious to add the Si group onto the hcpt of the Lavergne et al reference.

GROUPING OF THE CLAIMS

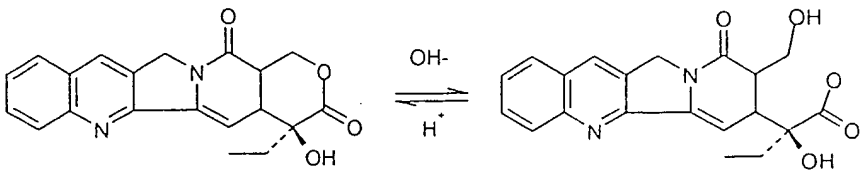
All of the claims stand or fall together.

APPLICANTS' ARGUMENTS

Applicants respectfully request that the Board of Patent Appeals and Interferences reverse the Examiner's rejection since it is deemed that the combination of the references, which the Examiner has made with the benefit of Applicants' disclosure, would in no way suggest to one skilled in the art Applicants' novel compounds and their use. The Hausheer et al reference teaches cpt compounds wherein R_1 can be one of a wide variety of substituents. R_1 can be acyl of an alkanoic acid, acyl of an alketic acid or alkynyl acid or an aryl acid or it can be alkenyl or alkynyl optionally substituted with at least one halogen or hydroxyl alkyl or alkoxy group or it can be halo, oxo or $-S-R_3$ or $-S(O)$-alkyl or $-OSO_2CF_3$ or $-SiR_8R_9R_{10}$ or-$R_5SiR_8R_9R_{10}$ or $-S-R_5-SiR_8R_9R_{10}$ which groups are said to make the cpt compounds more soluble. There is no teaching of any specific Si substituent and there is no indication of any advantage over the other possible substituents.

The Lavergne et al reference cited by the Examiner merely states that certain hcpt compounds having in Applicants' substitution position, X which can be hydrogen or ethyl and teaches that the ß-hydroxy lactone compound B 80245 which is unsubstituted in Applicants' position is a much weaker electrofilli than cpt and is a potent inhibitor of topoisomerase I activity and a potent cyctotoxic agent.

The Hausheer et al reference discloses lipophilic cpt derivatives. As well known to those skilled in the art, cpt shows a rapid and pH dependent hydrolysis of the lactone moiety to form an open E-ring with a hydroxy carboxylic acid function as follows:



The cpt carboxylate form (water-soluble form corresponding to the opened E-ring) is recognized by Hausheer as being less active than the lactone form. As noted in lines 11 to 18 of page 8, "The resulting cpt derivative carboxylate species will be water-soluble and have substantially reduced antineoplastic activity and...and is not the preferred form of the drug. The inventors submit that the lactone E-ring species of cpt (and its derivatives) is the preferred form of the drug for administration to subjects with

cancer." Also, in lines 1 to 5 of page 9, it is stated "Since..., the carboxylate species of cpt derivatives are predicted to have lower bioavailability than cpt derivatives which have the lactone E-ring." Therefore, the inventors of the reference in an attempt to obtain active cpt derivatives with the lactone E-ring, suggested cpt derivatives with lipophilic substituents.

The introduction of a lipophilic group increases the lipophilicity of the molecule and displaces the equilibrium on the side of the closed E-ring and this displacement leads to the protection of the active lactone formed from hydrolysis. This is taught in lines 33 of page 3 through line 2 of page 4 "Further, being highly lipophilic, they can be administered in the active lactone form and will have superior bioavailability relative to water soluble cpt derivatives." This was already shown in the stabilization of the lactone moiety of CP drugs by Burke et al (Biochemistry, 1993, Vol. 32, pp. 5352-5364, a copy of which is of record).

In contrast to the cpt, the key features of the hcpt derivatives is the best stability in a slow and irreversible E-ring opening. Thus, with hcpt, there is no stability problem or equilibrium problem to solve. This can be seen from Cancer Research. Vol. 59, pp. 2939-2943, a copy of which is of record. Thus, with these differences, the transposition of specific problems of a cpt derivative to hcpt is impossible since they are non-equivalent structures.

In order to demonstrate the non-equivalence between these two types of structures, Applicants have submitted a copy of Biochemistry, 1999, Vol. 38, pp. 15555-155563 which compares the cpt 6-membered ring with hcpt 7-membered rings. This study shows that the cleavage sites of the DNA by cpt and hcpt are different in their molecular environment. Therefore, one could not reasonably consider any equivalence between cpt and hcpt. All of these differences are also discussed in another publication entitled Current Pharmaceutical Design, 2002, Vol. 8, pp. 2505-2020, a copy of which is of record. The Board's attention is directed particularly to the first column of page 2509 as well as the relationship between the lipophily and stability of cpt derivatives and it goes on into the second column of page 2509. For all of these reasons, one skilled in the art would not apply the teachings obtained with cpt derivatives with the structure activity relationship of hcpt derivatives. Therefore, Hausheer et al is not relevant to present invention and the combination of the prior art fails. Therefore, withdrawal of this ground of rejection is requested.

To illustrate the unexpected effect of the compounds of the present invention, Applicants are submitting herewith the experimental results (IC_{50}) extracted from the present invention. Compounds of Formula I_A having a silyl radical are compared to very close compounds described in the present invention without the silyl group.

Ex	R_3	R_4	R_5	IC_{50}
17	F	F	$-(CH_2)_2SiMe_3$	5,0
13	F	F	Bu	8,5
11	F	F	Phe	12
22	H	H	$-(CH_2)_2SiMe_3$	8,6
5	H	H	Bu	16
7	H	H	Phe	13

It the table, R_2 and R_5 are both hydrogen and R_1 is ethyl. It can be seen that the substitution of a butyl or phenyl group by a $-(CH_2)_2SiMe_3$ with the same substituents at the other positions increases in an unexpected way the IC_{50} which means that a substantial increase in the activity of the corresponding Si compounds.

Applicants have clearly shown that hcpt and cpt compounds are non-equivalent structures and in contrast to cpt, the key feature of Applicants' cpt derivatives is their better stability and a slow and irreversible E-ring opening and with hcpt, there is no stability problem or equilibrium problem to solve. The record clearly shows that the two structures are non-equivalent and one would not combine the teaching of a cpt reference with an hcpt reference.

CONCLUSION

Therefore, it is believed that Applicants have complied with all the requisites for the granting of Letters Patent and it is requested that the Board of Patent Appeals and Interferences reverse the Examiner's rejection since one skilled in the art would not combine the references as the Examiner has done with the benefit of Applicants' disclosure. Three copies of the brief on appeal are being filed as well as PTO Form-2038 authorizing the $330.00 fee for filing the appeal brief.

Respectfully submitted,
Muserlian, Lucas and Mercanti

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CAM:ds
Enclosures

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APPENDIX

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Sir:

The claims in the application are:

Claim 5.

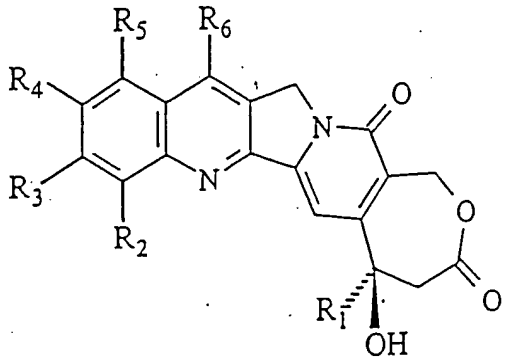
A compound of claim 24 selected from the group consisting of

(5R)-5-ethyl-9,10,difluoro-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1H,3H-oxepino [3',4':6,7]-indoloizino[1,2-b]quinoleine-3,15-dione;

(5R)-5-ethyl-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1H,3H-oxepine [3',4':6,7]indolizino[1,2-b]quinoleine-3,15-dione.

Claim 24.

A compound selected from the group consisting of the formula



(II_A)

wherein $R_1$is lower alkyl, R_2, R_3, R_4 and R_5 are individually selected from the group consisting of hydrogen, halogen and $-OSO_2R_{10}$, R_6 is $-(CH_2)_m$-$SiR_7R_8R_9$, R_7, R_8 and R_9 are individually lower alkyl, R_{10} is lower alkyl unsubstituted or substituted with at least one halogen or aryl unsubstituted or substituted with at least one lower alkyl, m is an integer from 0 to 6 and its non-toxic, pharmaceutically acceptable salts.

Claim 26,

An antitumoral composition comprising an antitumorally effective amount of a compound of formula (II_A) of claim 24.

Claim 27

A method of treating tumors in warm-blooded animals comprising administering to warm-blooded animals in need thereof an antitumorally effective amount of a compound of claim 24.